United States Environmental Protection Agency

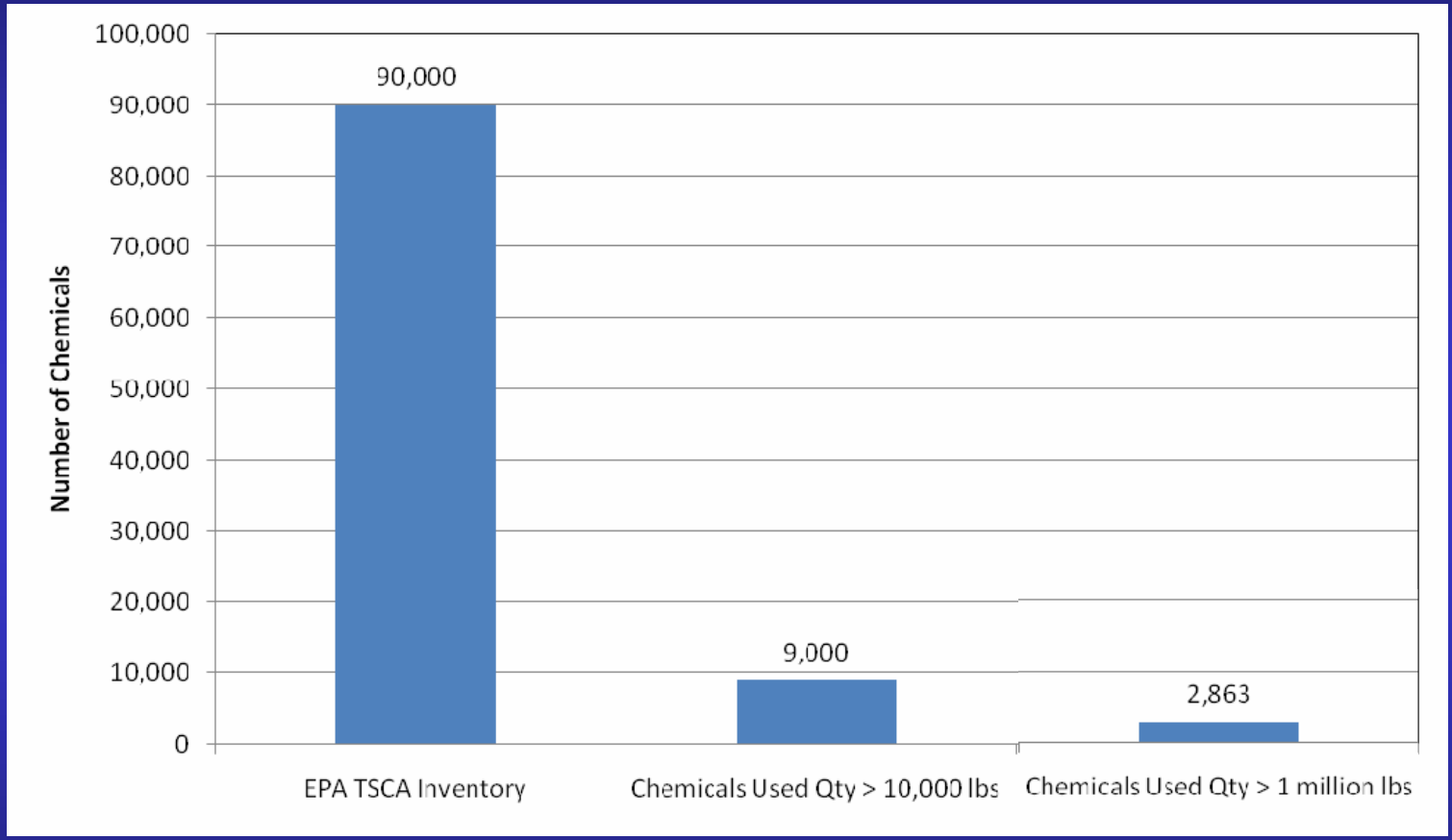
Using Genomics to Predict Potential Toxicity

International Science Forum on Computational Toxicology
RTP, NC
23 may 2007

Office of Research and Development
National Center for Computational Toxicology

Motivation

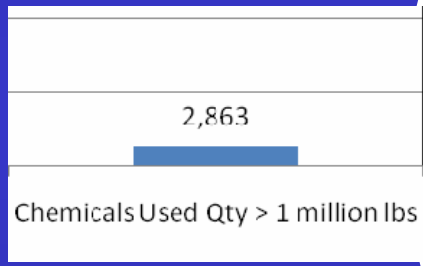
Environmental Toxicology

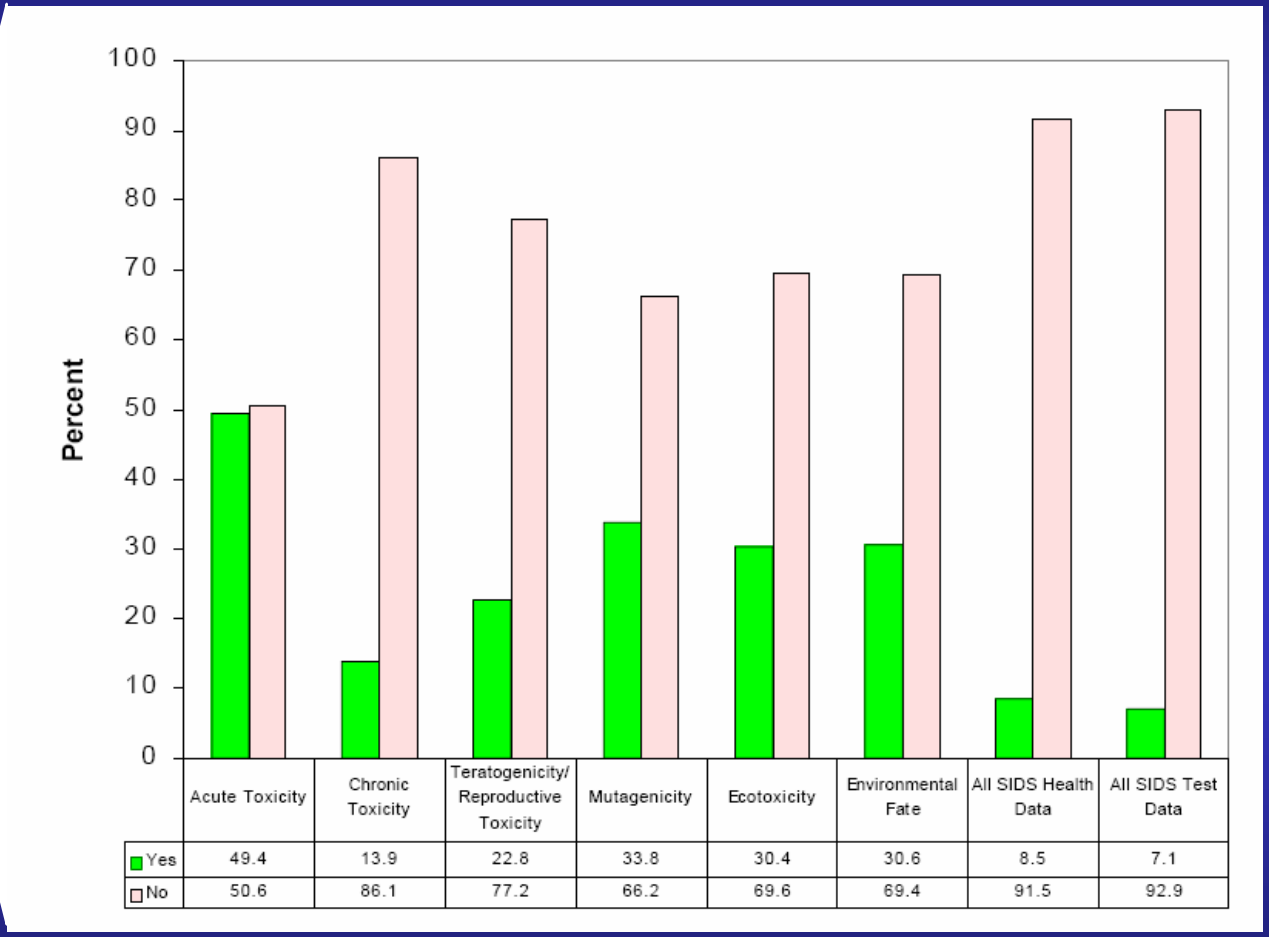


EPA OPPT Chem. Haz. Data Avail. Study, 1998

Motivation

Environmental Toxicology





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Motivation

Pharmaceutical Safety Assessment

- "About one-third of all drugs fail preclinical or clinical testing because of apparent or suspected drug toxicity. According to industry estimates, companies spend about $2 billion annual on toxicity-related drug failures." D&MD Market Analysis Report, "Managing Toxicology for the Future", 2003
- "...Clinical failures based on liver toxicity alone have cost them more than $2 billion in the last decade" FDA Critical Path White Paper, 2004
- "10% improvement in the prediction of drug failures would lead to a $100 million savings in development costs per drug" FDA Critical Path White Paper, 2004

Primary Goal of the Session

Present a broad spectrum of current efforts towards developing in vivo and in vitro genomic markers to predict complex toxicological endpoints...

10:30 AM – 10:35 AM	*Introduction – Predictive Toxicogenomics as a Component of the ToxCast Program* – **David Dix, U.S. EPA**
10:35 AM – 11:00 AM	*Identifying Gene Expression Biomarkers to Predict Rodent Cancer Bioassays* – **Rusty Thomas, The Hamner Institutes for Health Sciences**
11:00 AM – 11:25 AM	*Prediction System for Chemical Safety Using Percellome Toxicogenomics* – **Jun Kanno, National Institute of Health Sciences, Japan**
11:25 AM – 11:50 AM	*Application of In vitro Toxicogenomics towards Drug Safety Evaluation* – **Jeff Waring, Abbott Laboratories**
11:50 AM – 12:15 PM	*Characteristics of In Vivo and In Vitro Toxicogenomic Signatures Predictive of Toxicological Outcomes* – **Mark Fielden, Roche Palo Alto LLC**
12:15 PM – 12:30 PM	*Utility of Genomics and HTS Approaches for the Assessment of Industrial Chemicals* – **Philip Sayre, U.S. EPA/OPPT**

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Introduction – Predictive Toxicogenomics as a Component of the ToxCast Program

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David Dix

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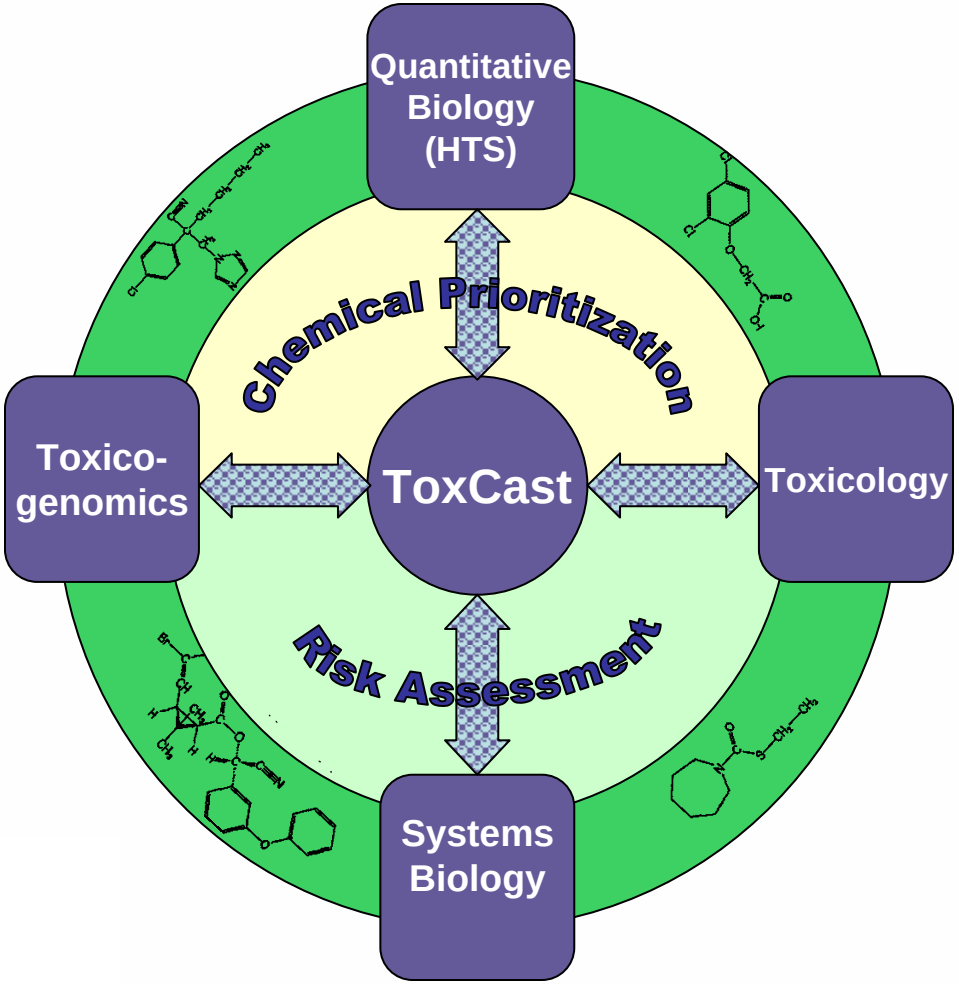
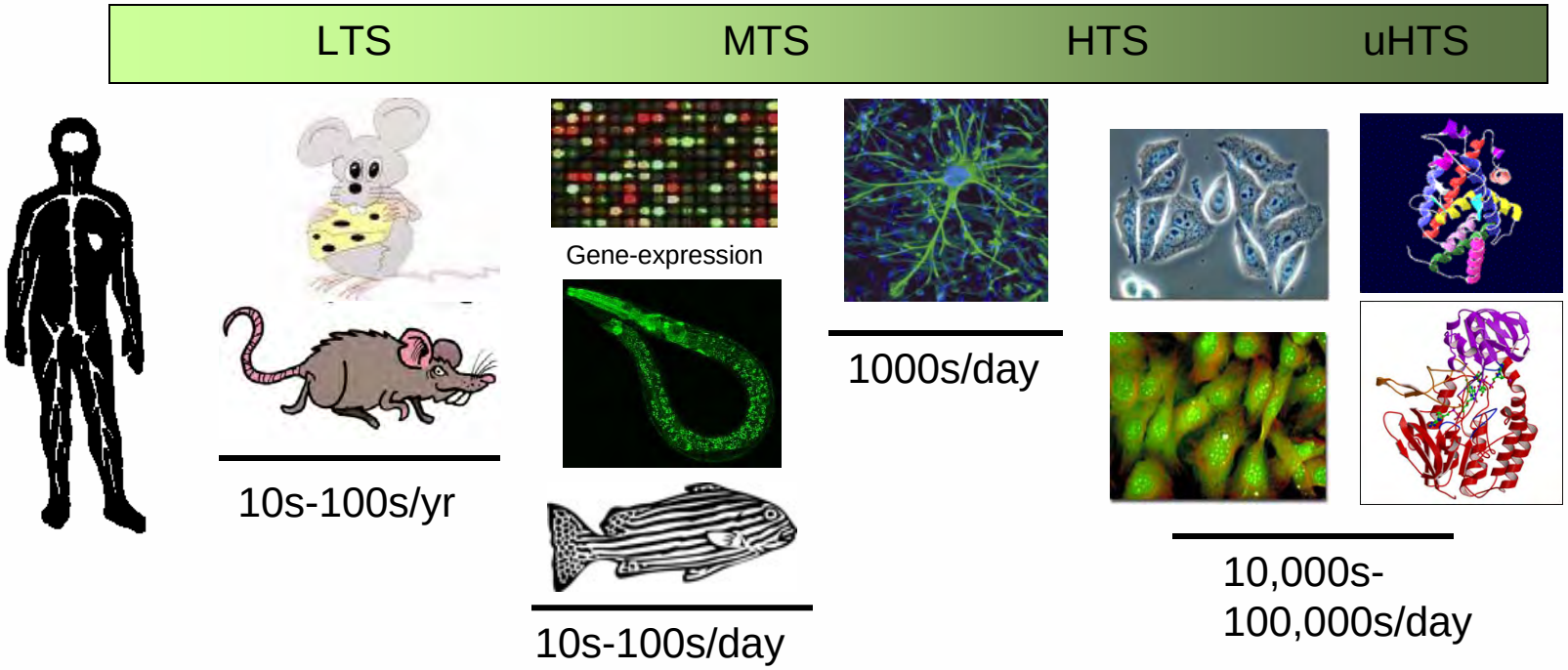
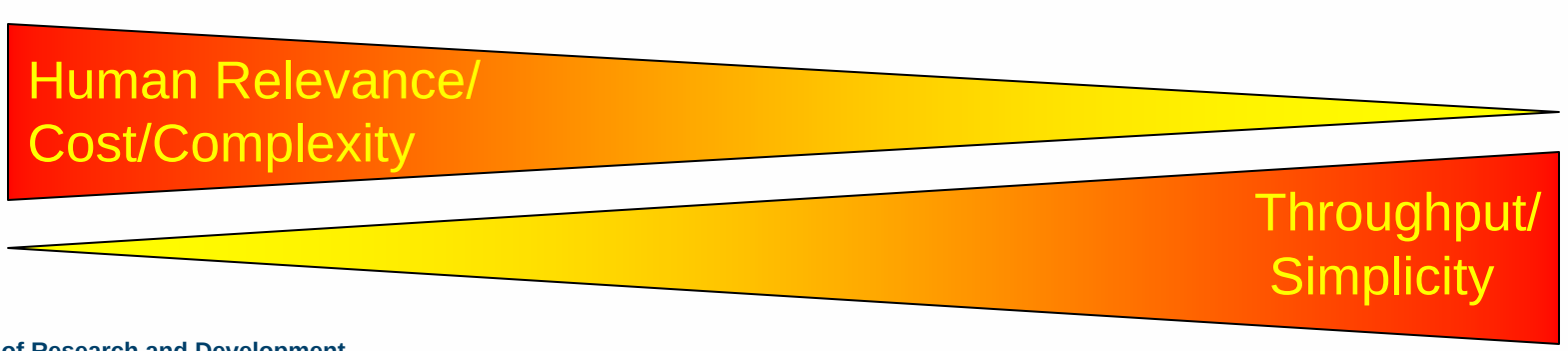
ToxCast Merges HTS and Genomics Technologies with Traditional Toxicology



High-Throughput Screening Assays

batch testing of chemicals for pharmacological/toxicological endpoints using automated liquid handling, detectors, and data acquisition





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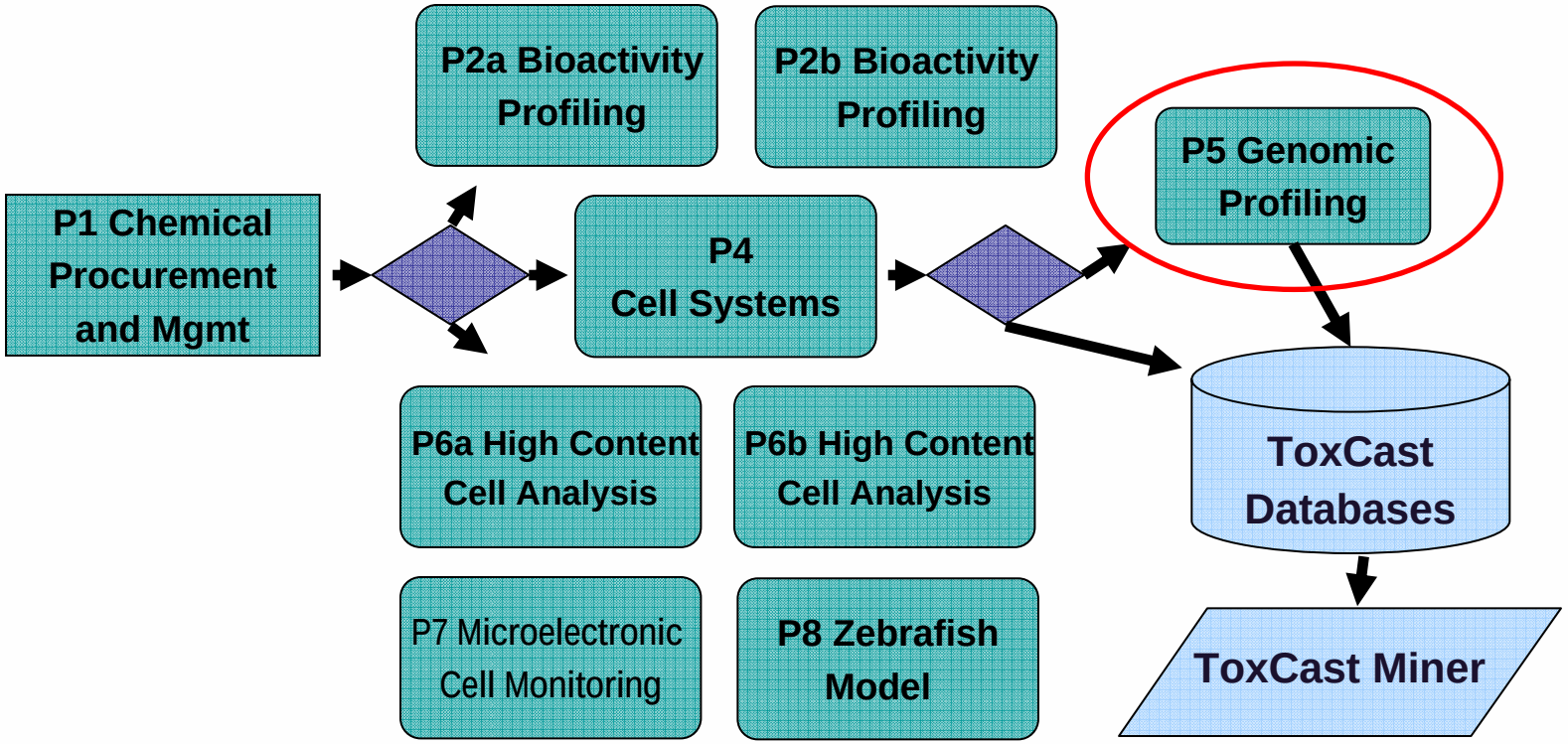
ToxCast Contracts for Data Generation



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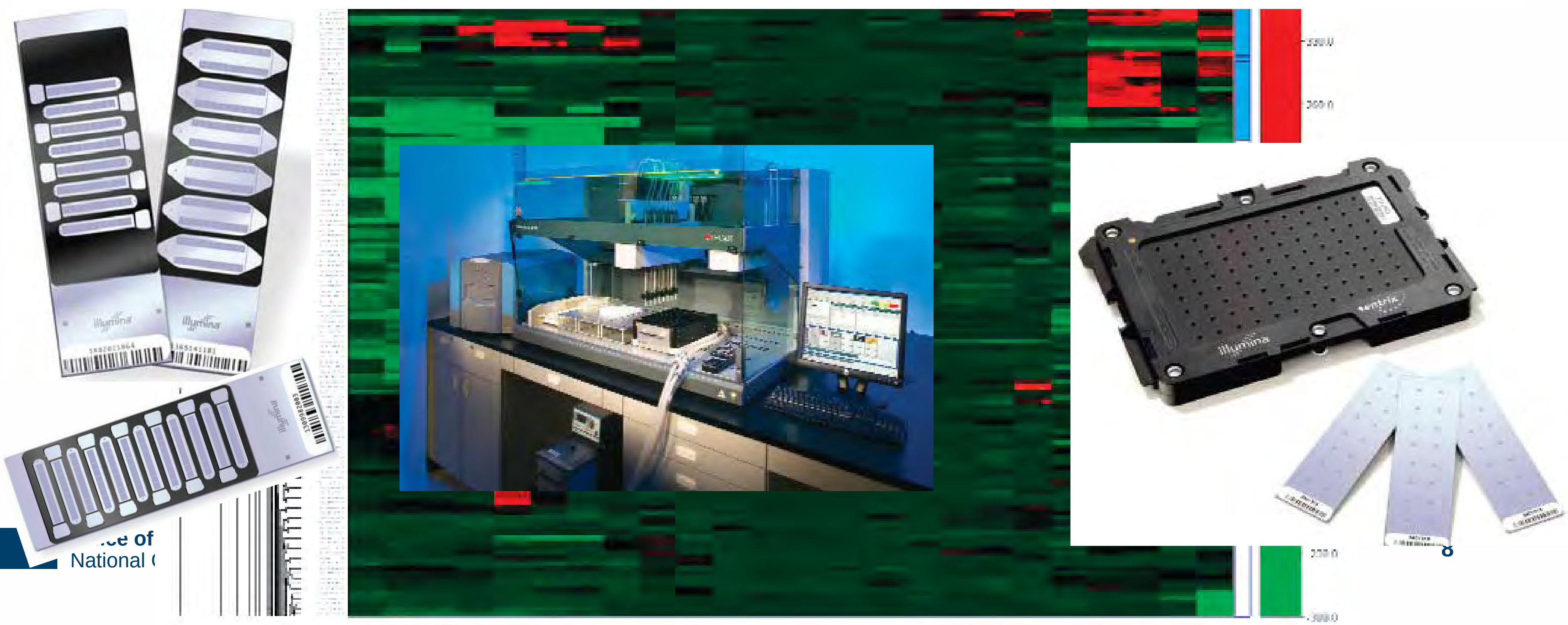
EXPRESSION ANALYSIS

Gene Expression Profiling by Microarray and PCR

Human BeadChips assay up to 48,000 transcripts.
Mouse BeadChips assay up to 47,000 transcripts.
RatRef BeadChips assay up to 22,000 transcripts.
Customized chips- up to 1400 genes in 96well format.
Individual or multiplexed PCR (≤ 48 transcripts in parallel).



Using Patterns in HTS, HCS and Genomics Data to Predict Toxicity

	Chemical			HTS			HCS			Genomics			Toxicity		
Chemical	Physico-Chemical Properties			In-vitro / Biochemical Assays			Cellular Assays			Gene Expression Signatures			Toxicity Endpoints		
	P1	…	PN	A1	…	AN	C1	…	CN	S1	…	SN	T1	…	TN
C1															
C2															
C3															
…															
CN															

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